Drug Combos Can Quell Refractory Hypertension

BY ROBERT FINN
San Francisco Bureau

ATLANTA — Stubbornly refractory hypertension can be approached with a number of drug combinations and other novel treatments, Dr. Angela L. Brown said at a meeting sponsored by the International Society on Hypertension in Blacks.

The combination of a diuretic and an inhibitor of the renin-angiotensin-aldosterone system (RAAS) is probably the most popular choice, said Dr. Brown of Washington University, St. Louis. This combination makes physiological sense because the two classes of drugs have complementary modes of action. As the diuretic decreases fluid volume, the RAAS inhibitor decreases pulmonary vascular resistance.

Furthermore, RAAS inhibitors counteract the relative increase in blood pressure resulting from diuretic-induced renin secretion. The combination is well tolerated, and it's effective in low-renin populations and African Americans.

Another popular combination is an ACE inhibitor along with a calcium channel blocker (CCB). The ACE inhibitor blocks the renin-angiotensin system, is effective in high-renin hypertension, works in all populations—especially whites, Hispanics, and young patients—and produces arterial and venous vasodilation. The CCB blocks the sympathetic nervous system, provides excellent efficacy, produces arterial vasodilation, is effective in low-renin hypertension, and works in all populations—particularly African Americans and the elderly.

Theoretically, an ACE inhibitor along with an angiotensin II receptor blocker (ARB) should also work, since they would provide intervention at two points in the RAAS cascade, and the use of an ARB may block angiotensin II formed through the non–ACE-dependent pathway. But in reality, studies have not shown enhanced blood pressure reduction, although the combination does significantly reduce proteinuria levels.

The combination of a diuretic and a RAAS inhibitor is well tolerated, and it's effective in low-renin populations and African Americans.

The combination of a dihydropyridine CCB (such as amlodipine, nifedipine, or isradipine) along with a nondihydropyridine CCB (such as verapamil or diltiazem) may actually be more effective. The dihydropyridines are less likely to decrease cardiac output and may cause an acute reflux tachycardia. The nondihydropyridines decrease the pulse rate and may have a negative inotropic effect. The nondihydropyridines also inhibit the cytochrome P450 system and slow metabolism of the dihydropyridine CCBs. There's good evidence that this combination does decrease blood pressure, Dr. Brown said.

Two other novel treatments for refractory hypertension—insulin sensitizers or statins—take common comorbidities into account. "Most of the patients I see don't just come in with hypertension," Dr. Brown said. "Maybe it's the blood pressure that gets them in the door, but when you get there and inspect them, they have dyslipidemia, they're obese, they have insulin resistance, [or] they have other cardiovascular risk factors that we have to treat."

Thiazolidinedione insulin sensitizers bind to peroxisome proliferator-activated receptor gamma (PPARγ) in muscle and fat to decrease insulin resistance. Studies have shown that such receptors are also plentiful in the kidney and that two mutations in the PPARγ gene are associated with severe hypertension in humans. Pioglitazone appears to result in significant decreases in systolic blood pressure in clinical trials.

The statins reduce cholesterol, are atheroprotective and stabilize atherosclerotic plaques, have antioxidative effects, reduce inflammation and thrombus formation, and improve endothelial function. A small study has now shown that statins can reduce the magnitude of angiotensin-induced increases in blood pressure.

Nitrates are known to be effective for the acute treatment of severe hypertension and aortic dissection, but long-term use is hampered by tachyphylaxis and tolerance. Some studies have suggested, however, that intermittent dosing of long-acting nitrates resulted in a decrease in the augmentation index of the reflected pulse wave, thereby decreasing systolic blood pressure.

In addition to pharmacotherapy, there's at least one medical device that shows promise in treating refractory hypertension. The CVRx Rheos Baroreflex Hypertension Therapy System is an investigational implantable device that stimulates baroreceptors in the arterial walls of the carotid sinus. This simulates a rise in blood pressure that the brain works to counteract.

Studies have shown that the device causes a decrease in heart rate, a relaxation of blood vessels, and fluid release from the kidneys. Blood pressure in one patient was reduced from 186/98 mm Hg to 153/80 mm Hg in seconds by the use of the device. Dr. Brown, who disclosed that she has no ties to the manufacturer, said the device is well tolerated and causes no discomfort in patients.

She did disclose that she has received research support from GlaxoSmithKline and Novartis, is a consultant for Pfizer, and serves on speakers' bureaus for five pharmaceutical companies. The meeting was cosponsored by the American Society of Hypertension. ■

Metabolic Syndrome Ups Salt Sensitivity

BY ROBERT FINN
San Francisco Bureau

ATLANTA — People with metabolic syndrome have blood pressures that are more sensitive to salt than do people without the syndrome, according to a poster presentation by Dr. Luigi X. Cubeddu at a meeting sponsored by the International Society on Hypertension in Blacks.

His study, in 301 subjects with and without metabolic syndrome, showed that normal dietary salt intake induces large BP increases in people with the condition, making them "exquisitely sensitive to dietary salt.

"Salt restriction, in addition to exercise and caloric restriction, must be a fundamental part of the treatment plan for patients with the metabolic syndrome," wrote Dr. Cubeddu of Nova Southeastern University, Fort Lauderdale, Fla.

The subjects' average age was 42 years; 109 of them were diagnosed with metabolic syndrome in accordance with guidelines from the National Cholesterol Education Program. As expected, subjects with metabolic syndrome had significantly higher baseline BP than those without: 127/83 mm Hg, compared with 114/75 mm Hg.

The investigators measured blood pressure and several other physiologic signs during a week-long baseline period in which salt intake was normal (8 g/day), and also during a week of high salt intake (about 18 g/day) and a week of low salt intake (2.3 g/day).

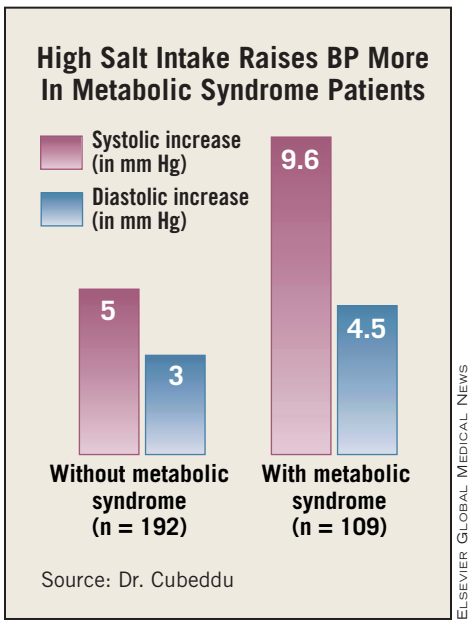
The high-salt condition resulted in increases in BP in both groups of subjects, but those with metabolic syndrome had significantly larger increases in both systolic and diastolic pressures. While the patients without metabolic syndrome increased their systolic BP an average of 5.0 mm Hg and their diastolic pressure an average of 3.0 mm Hg, those with metabolic syndrome experienced systolic and diastolic increases of 9.6 and 4.5 mm Hg, respectively.

The degree of salt sensitivity was also associated with the severity of metabolic syndrome. The more components of metabolic syndrome a subject had, the larger was his or her decrease in blood pressure associated with salt restriction.

Subjects with four or five components of metabolic syndrome saw decreases of 8.7 mm Hg systolic and 5.0 mm Hg diastolic in response to salt restriction, while those with just two of the traits saw decreases of 3.4 and 2.1.

The investigators noted that salt sensitivity is a gradual condition that worsens in parallel with metabolic syndrome, and that dietary salt is a major determinant of the increased prevalence of prehypertension and hypertension in such patients.

The meeting was cosponsored by the American Society of Hypertension. ■



ELSEVIER GLOBAL MEDICAL NEWS

Aldosterone-Apnea Link Found in Hypertensives

NEW YORK — A link between aldosterone, hypertension, and obstructive sleep apnea was established in a study with 71 patients.

"We found an extraordinarily high prevalence of obstructive sleep apnea in patients with [treatment-] resistant hypertension," and serum aldosterone levels were significantly related to the severity of sleep apnea," Dr. David A. Calhoun reported at the annual meeting of the American Society of Hypertension.

"We went in thinking that obstructive sleep apnea was driving aldosterone release, but now we think that a high serum level of aldosterone somehow contributes to worsening sleep apnea," said Dr. Calhoun, a hypertension specialist at the University of Alabama, Birmingham. The link may be mediated by increased salt and water retention or perhaps by a change in flow resistance.

Dr. Calhoun and his associates have begun a study to explore the implications of their findings for patient management. They are withholding continuous positive air pressure, a standard treatment for obstructive sleep apnea, from patients with the disorder and are instead treating them with spironolactone, an aldosterone antagonist. The goal is to see whether spironolactone alone is effective at relieving sleep apnea.

The current study involved a consecutive series of 41 men and 30 women who were referred to the hypertension clinic at UAB because of treatment-resistant hypertension. Their mean blood pressure was 156/88 mm Hg despite treatment with an average of four antihypertensive drugs.

The patients were assessed for obstructive sleep apnea by diagnostic polysomnography. The overall prevalence of obstructive sleep apnea was 85%, with a prevalence of 90% in the men and 79% in the women. The average apnea-hypopnea index for all patients was 24 apnea events per hour.

The patients with sleep apnea also had high serum and urine levels of aldosterone. Patients with the most severe sleep apnea had the highest levels, Dr. Calhoun said.

—Mitchel L. Zoler